REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

In the present Reply, claims 1-43 have been amended. This makes claims 1-43 as pending in the present application.

No new matter has been added by way of these amendments, because each amendment is supported by the present specification and/or editorial in nature. For example, the various amendments correct improper dependencies and provide proper antecedent basis. Thus, these are clarifying and not narrowing amendments. By deleting/amending these terms in order to clarify the claimed invention (e.g., "Pharmaceutical composition" to "The pharmaceutical composition"), Applicants are in no way conceding any limitations with respect to the interpretation of the claims under the Doctrine of Equivalents.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Election/Restriction

The Examiner has required election in the present application between:

Group I, claims 1-2 (in part), 3-6, 18-19 (in part) and 32-34;

Group II, claims 1-2 (in part), 18-19 (in part) and 35-36;

Group III, claims 1-2 (in part), 7-9, 18-19 (in part) and 37-38;

Group IV, claims 1-2 (in part), 10-13, 18-19 (in part) and 39-41;

Group V, claims 1-2 (in part), 14-17, 18-19 (in part) and 42-43;

Group VI, claims 20-23;

Group VII, claims 24-28; and

Group VIII, claims 29-30 (see pages 2-3 of the Office Action).

Election with Traverse

For the purpose of examination of the present application, Applicants elect, **with traverse**, Group I, claims 1-2 (in part), 3-6, 18-19 (in part) and 32-34. The basis for the traversal is as follows.

The Examiner states that Groups I-V are different inventions from one another as they "are drawn to different polymorphs of idazoxan that are characterized by different X-ray diffraction spectrums" (see the paragraph bridging pages 3-4 of the Office Action). However, the specified Groups claims are not "different polymorphs and instead, Groups I-V are related. To support Applicants' position, Applicants herein enclose an excerpt from *Wikipedia* (total of 2 pages). The attached *Wikipedia* excerpt explains which polymorphs are important and their importance in the pharmaceutical industry.

Also, the Examiner cites M.P.E.P. § 806.06 in the Office Action in separating the claims into Groups I-V. However, Applicants note that this part of the M.P.E.P. considers (i) an article of apparel versus a locomotive bearing, and (ii) a method of painting versus a method of boring a well, as examples of distinct inventions. The instantly disputed claims do not belong in such extreme classifications. Thus, the instant classification and separation of Groups I-V is improper. Reconsideration and withdrawal of this Restriction Requirement are respectfully requested.

Regarding Groups VI-VIII, these are claims directed to the application of the polymorphs of idazoxan. Specifically, the claims are directed to: tablets comprising pharmaceutical compositions (see claims 20-23), processes for manufacturing said tablets (claims 24-28) and methods of treatment of cerebral pathologies with the composition containing one or more polymorphs of idazoxan (claims 29-31; Applicants respectfully refer the Examiner to how these claims have been amended herein). Further, all of these claims ultimately depend on claim 1. Thus, the applications are clearly closely related to one another.

Additionally, the Examiner cites M.P.E.P. § 806.06 in the Office Action in separating the claims into Groups VI-VIII. However, again, Applicants note that this part of the M.P.E.P. considers (i) an article of apparel versus a locomotive bearing, and (ii) a method of painting versus a method of boring a well, as examples of distinct inventions. Thus, the instant classification and separation of these Groups is also improper.

Accordingly, for any and all of the reasons stated above, rejoinder of the Groups is warranted and respectfully requested.

Conclusion

An early and favorable action on the pending claims is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Dated: NOV 3 0 2006

Respectfully submitted,

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Attachment: Excerpt from *Wikipedia* (2 pages)

Polymorphism (materials science)

From Wikipedia, the free encyclopedia

Polymorphism in materials science is the ability of a solid material to exist in more than one form or crystal structure. Polymorphism can potentially be found in any crystalline material including polymers and metals and is related to allotropy which refers to elemental solids. Together with polymorphism the complete morphology of a material is described by other variables such as crystal habit, amorphous fraction or Crystallographic defects. Polymorphism is relevant to the fields of pharmaceuticals, agrochemicals, pigments, dyestuffs, foods and explosives.

When polymorphism exists as a result of difference in crystal packing it is called **packing polymorphism**. Polymorphism can also result from the existence of different conformers of the same molecule in **conformational polymorphism**. In **pseudopolymorphism** the different crystal types are the result of hydration or solvation. An example of an organic polymorph is glycine which is able to form monoclinic and hexagonal crystals.

An analogous phenomenon for amorphous materials is polymorphism, when a substance can take on several different amorphous modifications.

Contents

Polymorphism in pharmaceuticals

Polymorphism is important in the development of pharmaceutical ingredients. Many drugs are receiving regulatory approval for only a single crystal form or polymorph. In a classic patent case the pharmaceutical company GlaxoSmithKline defended its patent for the polymorph type II of the active ingredient in Zantac against competitors while that of the polymorph type I had already expired. Polymorphism in drugs can also have direct medical implications. Medicine is often administered orally as a crystalline solid and dissolution rates depend on the exact crystal form of a polymorph.

Despite the potential implications polymorphism is not always well understood. In 2006 a new crystal form was discovered of maleic acid 124 years after the first crystal structure determination [1] (http://en.wikipedia.org/wiki/Polymorphism_(materials_science)#endnote_Day). Maleic acid is a chemical manufactured on a very large scale in the chemical industry and is a salt forming component in medicine. The new crystal type is produced when a caffeine - maleic acid co-crystal (2:1) is dissolved in chloroform and when the solvent is allowed to evaporate slowly. Whereas form I has monoclinic space group $P2_1/c$, the new form has space group Pc. Both polymorphs consist of sheets of molecules connected through hydrogen bonding of the carboxylic acid groups but in form I the sheets alternate with respect of the net dipole moment whereas in form II the sheets are oriented in the same direction.

1,3,5-Trinitrobenzene is more than 125 years old and was used as an explosive before the arrival of the safer 1,3,5-trinitrotoluene. Only one crystal form of 1,3,5-trinitrobenzene has been known in the space group Pbca. In 2004, a second polymorph was obtained in the space group Pca2(1) when the compound was crystallized in the presence of an additive, trisindane. This experiment shows that additives can induce the appearance of polymorphic forms.

Polymorphism is also established for acetylsalicylic acid [2] (http://en.wikipedia.org/wiki/Polymorphism_

(materials_science)#endnote_Vishweshwar). A new crystal type was found after attempted co-crystallization of aspirin and levetiracetam from hot acetonitrile. Form II is only stable at 100 K and reverts back to form II at ambient temperature. In form I two salicylic molecules form centrosymmetric dimers through the acetyl groups with the (acidic) methyl proton to carbonyl hydrogen bonds and in the newly discovered form II each salicylic molecule forms the same hydrogen bonds but then with two neighboring molecules instead of one. With respect to the hydrogen bonds formed by the carboxylic acid groups both polymorphs form identical dimer structures.

Trivia

McCrone's Law states that *every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound.*

Crystal Polymorphs can disappear. There have been cases of individual laboratories growing one crystal form. They then grow a different crystal form, and are unable to make the first form again. Alternatively, they find that they can make the first form again but it now converts to the second form over time. The drug Paroxetine was subject to a law suit that hinged on such a pair of polymorphs (A link to a discussion of cases in Canada and the US has been given below).

References

1. ↑ *Investigating the latent polymorphism of maleic acid* Graeme M. Day, Andrew V. Trask, W. D. Samuel Motherwell and William Jones Chemical Communications, **2006**, (1), 54 - 56 DOI: 10.1039/b513442k Abstract (http://www.rsc.org/publishing/journals/CC/article.asp?doi=b513442k)
2. ↑ *The Predictably Elusive Form II of Aspirin* Peddy Vishweshwar, Jennifer A. McMahon, Mark Oliveira, Matthew L. Peterson, and Michael J. Zaworotko J. Am. Chem. Soc.; **2005**; 127(48) pp 16802 - 16803; (Communication) DOI: 10.1021/ja056455b Abstract (http://pubs3.acs.org/acs/journals/doilookup?in_doi=10.1021/ja056455b)

External links

- "Small Molecule Crystalization" (http://acaschool.iit.edu/lectures04/JLiangXtal.pdf) (PDF) at Illinois Institute of Technology website
- "A discussion of crystal form litigation to develop generic versions of (http://www.blakes.com/english/publications/brip/article.asp?A_ID=169&DB=blakesProperty) Paroxetine "

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Category: Materials science